

### **Remarks**

Applicant appreciates the thorough examination of the present application as evidenced by the Office Action dated December 31, 2003 (hereinafter, the "Office Action").

Claims 22-24, 31, 32, 37, 44, 49 and 51-53 are pending in the present application. Claims 22-24, 31, 32, 37, 44, 49 and 51-53 stand rejected. Applicant further confirms that Applicant's previous election in paper No. 12, i.e., (a) salt, particularly potassium sulfate, as the osmotically active compound, (b) cystic fibrosis as the disease afflicting the subject, and (c) inhalation as the administering method, should be applied to the application as pending under the present Request for Continued Examination.

The concerns raised by the Examiner in the Office Action are addressed below.

#### **I. Substance of the Interview**

As noted in Applicant's Amendment dated October 22, 2003, Applicant and the Applicant's representatives, Kenneth D. Sibley and Shawna Cannon Lemon, appreciated the opportunity to speak with the Examiner on June 4, 2003.<sup>1</sup> During this telephonic interview, the Examiner was introduced to the inventor, Dr. Richard C. Boucher, Jr. As the Examiner may recall, Dr. Boucher is currently a Professor of Medicine and the Director of the Cystic Fibrosis/Pulmonary Research and Treatment Center at the University of North Carolina at Chapel Hill School of Medicine, where he holds an endowed chair as a William Rand Kenan Professor.

As noted in the Examiner's Interview Summary accompanying the Office Action, during the telephonic interview, the Examiner requested information regarding the protocol for diagnosis of cystic fibrosis as it relates to U.S. Patent No. 5,817,028 to Anderson. This request was addressed in Applicant's Amendment dated October 22, 2003, the contents of which are incorporated herein by reference. The Examiner further requested evidence supporting Applicant's claim of enhanced efficacy. Applicant hereby provides the following response to address the Examiner's concerns regarding the above-referenced case.

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<sup>1</sup> The Amendment dated October 22, 2003 inadvertently listed June 6, 2003 as the date of the telephonic interview.

## **II. Rejection Under 35 U.S.C. § 103**

Claims 22-24, 31, 32, 37, 44, 49 and 51-53 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,817,028 to Anderson (hereinafter, "Anderson"), in view of U.S. Patent No. 5,876,700 to Boucher, Jr. et al. (hereinafter, "Boucher, Jr. et al.") and U.S. Patent No. 5,837,266 to Jungherr et al. (hereinafter, "Jungherr et al.") and in further view of Robinson et al. *Am. J. Respir. Crit. Care Med.* 153:1503-1509 (1996) (hereinafter, "Robinson") and Eng et al. *Ped. Pulmon.* 21:77-83 (1996) (hereinafter, "Eng et al."). More specifically, the Office Action states the following:

A person of ordinary skill in the art would have been motivated to treat a subject with cystic fibrosis by administering to the subject a combination of osmolyte, such as potassium sulfate and a sodium channel blocker, such as benzamil or phenamil because it is prima facie obvious to combine two agents each of which is taught in the prior art to be useful for same purpose in order to form a third composition that is used for the very same purpose; idea of combining them flows logically from their having been individually taught in prior art; thus, the claimed invention which is drawn to a method for treating cystic fibrosis, sets forth prima facie obvious subject matter.

Office Action, page 4. Applicant respectfully disagrees with this assertion.

A thorough review of the cited references reveals the following:

(a) **Anderson:** Anderson merely describes a method for testing the susceptibility of a person to asthma. Moreover, as noted by the Examiner, "Anderson does not teach expressly the employment of the method for treating cystic fibrosis, or administering a sodium channel blocker agent with an osmolyte for treating cystic fibrosis, or employ potassium sulfate as the osmolyte." Office Action, page 3;

(b) **Boucher, Jr. et al.:** Boucher, Jr. et al. discloses methods of hydrating lung mucous secretions in the lungs of a subject involving administering benzamil or phenamil to the lungs. The method is useful in the treatment of diseases such as cystic fibrosis and chronic bronchitis. *See* Abstract, Boucher, Jr. et al;

(c) **Jungherr et al.:** Jungherr et al. presents a sustained release drug delivery composition comprising microspheres containing a pharmaceutically active agent, a core of a ion-exchange resin and a polymeric coating completely surrounding the core wherein the coating is water-insoluble and hydrolytically

stable in physiological environments. *See* Abstract. Moreover, Jungherr et al. is particularly directed to ocular delivery systems. *See* Jungherr et al., Field of the Invention;

(d) **Eng et al.**: Eng et al. suggests that short-term administration of inhaled hypertonic saline improves pulmonary function in children and young adults who have moderate to severe cystic fibrosis lung disease. *See* Eng et al., page 82, col. 2; and

(e) **Robinson et al.**: Robinson et al. concludes that inhalation of hypertonic saline is a potentially useful treatment in patients with cystic fibrosis.

None of the cited references teach or suggest a method of **administering an active therapeutic agent to an airway surface** of a subject in need thereof, comprising administering the active agent in an effective therapeutic amount in a vehicle, which vehicle comprises an osmotically active compound, the osmotically active compound included in an amount effective to increase the volume of liquid on the airway surface as recited in claim 1. Additionally, none of the cited references teach or suggest a method of administering a sodium channel blocker to an airway surface of a subject in need thereof, comprising administering the sodium channel blocker in an effective therapeutic amount in a vehicle, said vehicle comprising potassium sulfate as an ionic osmolyte, said potassium sulfate included in an amount effective to increase the volume of liquid on the airway surface as recited in claim 51.

Further, Applicant respectfully submits that one of ordinary skill in the art would not have been motivated to combine the active agents of the present invention with an ionic osmolyte for **administration of an active therapeutic agent to an airway surface** where as noted above, the cited references are clearly not directed to **administration of an active therapeutic agent to the airway surface.**

The Office Action asserts that Eng et al. "teaches specifically the usefulness of osmolytes (as hypertonic solution) in mucociliary clearance and in providing treatment of cystic fibrosis (Office Action, page 3), it should be noted that Eng et al. merely discusses the short-term efficacy of hypertonic **saline** on pulmonary function in patients with cystic fibrosis. Moreover, where the Office Action asserts that Robinson et al. "teaches the

usefulness of hypertonic saline in combination with amiloride, a sodium channel blocking agent" (Office Action, page 3), it should be further noted that Robinson et al. showed that only hypertonic saline promoted mucus clearance and that neither amiloride nor amiloride and hypertonic saline significantly improved mucociliary clearance. See Eng et al. page 1506, col. 2. Again, the cited references do not relate to administration of active therapeutic agents to an airway surface.

Accordingly, Applicant respectfully submits that claims 22-24, 31, 32, 37, 44, 49 and 51-53 are not unpatentable under 35 U.S.C. § 103(a) in view of the cited references and respectfully request that this rejection be withdrawn.

### **III. Response to the Arguments**

As noted above, Applicant appreciates the thorough review of the present application as further evidenced by the "Response to the Arguments" section presented in the Office Action. In this section, however, the Office Action states that "Robinson and Eng provide further evidence that using osmotically active agents for increasing mucociliary clearance or inducing sputum is a known method for treating cystic fibrosis." Office Action, page 5. Applicant respectfully submits that the Examiner has mischaracterized an embodiment of the present invention.

As noted above, the cited references merely present the short-term effects of hypertonic saline on pulmonary function in patients with cystic fibrosis (Eng et al.) or the acute effects of hypertonic saline, amiloride, or hypertonic saline and amiloride on mucociliary clearance in patients with cystic fibrosis. These short-lived effects mentioned in the cited references do not teach or suggest the present invention directed to methods of **administering an active therapeutic agent to an airway surface** of a subject in need thereof.

Although Applicant respectfully submits that a *prima facie* case of obviousness has not been established, Applicant hereby submits an unsigned Declaration of Dr. Richard C. Boucher, Jr. Under 37 C.F.R. § 1.132 (hereinafter, "Declaration of Dr. Boucher, Jr."). A signed copy of the Declaration of Dr. Boucher, Jr. will be submitted forthwith. The Declaration of Dr. Boucher, Jr. provides unexpected results that show an increase in drug penetration associated with the methods of the present invention.

Figure 1 illustrates studies wherein well-differentiated cystic fibrosis bronchial epithelia were loaded with 5  $\mu$ M Snarf (Molecular Probes, USA) to denote the cell cytosol, red in color (Panel A). Isotonic solution (1.5  $\mu$ L) was added to the apical surface of a thickened mucus layer followed by fluorescein 20  $\mu$ M (green in color, Panel B). Panel B image was captured 5 min post fluorescein addition. Applicants note that the drug surrogate was trapped in thickened mucus and access to epithelial surface (and epithelial uptake) was restricted. No cellular uptake was detectable. Applicant further notes that fluorescein was employed in this assay for the molecular weight similarity to that of amiloride (332 compared to 266, respectively,) and assists in the visualization of mucus viscosity and its significance in drug transport.

Figure 2 illustrates the same method as applied in Figure 1, except a hypertonic solution (~300 mM potassium phosphate) was added to the apical surface rather than isotonic saline. Hypertonic solution swelled the mucus, allowing the drug surrogate (fluorescein) to penetrate to the cell surface, following which there was rapid cellular uptake of the surrogate.

Thus, embodiments of the present invention provide enhanced drug penetration through the thickened mucus to the cell surface, and thus, provide methods of administering an active therapeutic agent to an airway surface of a subject in need thereof.

In sum, embodiments of the present invention provide methods of administering an active therapeutic agent to an airway surface of a subject in need thereof. In contrast, the cited references are not directed to such methods of administering an active therapeutic agent to an airway surface.

Accordingly, Applicant submits that claims 22-24, 31, 32, 37, 44, 49 and 51-53 are not obvious in view of Anderson, Boucher, Jr. et al., Jungherr et al. and in further view of Robinson et al. and Eng et al. and respectfully requests that this rejection be withdrawn.

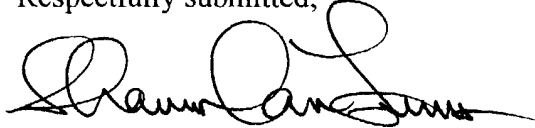
### **III. Conclusion**

In view of the foregoing amendments and remarks, Applicants respectfully request that all outstanding rejections to the claims be withdrawn and that a Notice of Allowance be issued in due course. The Examiner is invited and encouraged to contact the undersigned directly if such contact will expedite the prosecution of the pending claims to issue. In any event, any questions that the Examiner may have should be directed to the undersigned, who may be reached at (919) 854-1400.

In re: Boucher, Jr.  
Serial No.: 09/465,429  
Filed: December 21, 1999  
Page 9 of 9

No fee is believed due. However, the Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, to Deposit Account No. 50-0220.

Respectfully submitted,



Shawna Cannon Lemon  
Registration No. 53,888

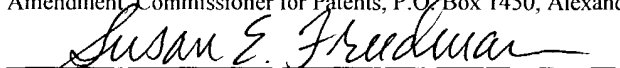
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Susan E. Freedman

Date of Signature: March 31, 2004